Knoll Pharmaceutical Company

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Dockets Management Branch
HFA-305
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Draft Guidance for Industry on
BA and BE Studies for Orally
Administered Drug Products -
General Considerations
Docket No. 99D-2729

Knoll Pharmaceutical Company ("Knoll") believes that this draft guidance is generally useful and appropriate for most orally administered drug products, but that the draft guidance errs in its tacit assumption that once this draft document is finalized it will not be necessary to issue a drug-specific BE guidance for orally administered levothyroxine sodium drug products. Knoll believes that a guidance tailored to the complexities of levothyroxine sodium BE studies will be necessary, and asks that FDA not rule out that possibility until it has considered the matter more thoroughly.

Among the issues which will need to be considered in connection with BE studies of LT4 drug products are the following:

1. As FDA has already recognized, levothyroxine is a narrow therapeutic index drug. 62 Fed. Reg. 43538 (August 14, 1997); prolonged administration of too much or too little LT4 can be problematic in causing over- or under-suppression of TSH.[1] Recognizing this, physicians often aim to keep their patients' TSH levels within narrow bounds. They and their patients must be assured that not only the product initially prescribed but also any product which is said to be therapeutically equivalent to it will keep TSH levels where the physician

1. Despite FDA's calling levothyroxine sodium a narrow therapeutic index drug in its Federal Register notice, the draft guidance omits levothyroxine sodium from the list of narrow therapeutic index drugs on page 21. The omission should be remedied in any final guidance.

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intended them. At present, expert thyroidologists recommend that patients be retested and retitrated, if need be, whenever one product is substituted for another.[2] Before any two LT4 products are declared therapeutically equivalent, thus, in FDA's view, obviating the need for retesting and retitration at the time of substitution, clinicians and patients will want and should have assurance that not just T4 but also TSH levels are comparable - and comparable within the narrow bounds appropriate for a narrow therapeutic index drug.

2. Under the Food, Drug, and Cosmetic Act and FDA's implementing regulations, the conclusion that one drug is equivalent to another must be based on studies of "appropriate design." Despite much debate on the subject, numerous aspects of appropriate design for studies of levothyroxine drug products remain to be resolved. For example, should such studies be conducted in athyreotic patients? If they are conducted in patients who do or might have some functioning thyroid, how should/can endogenous production of LT4 be distinguished from exogenous drug? Should data be adjusted for baseline values? Should the studies be single dose or multiple dose? Can a study in which T4 is comparable but TSH is not be considered appropriate?

3. Like the design of BE studies of levothyroxine, conduct of such studies must also be appropriate. If investigators fail to take blood samples at the same time each day in each patient, diurnal variability could confound the study. Similarly, the timing of food intake with respect to the dose can be important because food affects absorption of LT4. In this regard, Knoll suggests that FDA's Division of Bioresearch Monitoring should be required to check each BE study of levothyroxine to make sure that the apparent comparability of two products is real, not the result of a poorly conducted study.

4. The draft guidance states on page 5 that "similar approaches to establishing BA in an NDA should generally be followed in assessing BE . . ." In the case of levothyroxine, that is not necessarily so. In its draft guidance on bioavailability studies for levothyroxine,[3] FDA proposed to use a BA method modeled on the Berg-Mayor study design. As Knoll explained in comments on the draft guidance, the Berg-Mayor model is unsuitable for use in bioequivalence, among other reasons because it utilizes supraphysiologic doses which suppress TSH, making it impossible to assess whether two products produce comparable levels of TSH.[4]

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2. See, e.g., Singer et al., Treatment Guidelines for Patients with Hyperthyroidism and Hypothyroidism, JAMA 1995; 273:808-12 (these guidelines were prepared by the Standards of Care Committee of the American Thyroid Association); and American Association of Clinical Endocronologists, AACE Clinical Practice Guidelines for the Evaluation and Treatment of Hyperthyroidism and Hypothyroidism, Endocrine Practice 1995; 1:54-62 (also available on the Internet at "http://www.aace.com/clin/guides/thyroid_guide.html").

3. Docket No. 99D-1149, 64 Fed. Reg. 31280 (June 10, 1999).

4. A copy of Knoll's comments, without attachments, is attached.

Thus, even if FDA does adopt the Berg-Mayor model for BA, it should not do so for BE studies of levothyroxine.

In light of such considerations, Knoll urges FDA not to take the "one size fits all" approach to BE studies of levothyroxine, but, instead, to consider these issues separately and carefully.

Sincerely,

Robert W. Ashworth /91

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Dockets Management Branch (HFA-305)
Food and Drug Administration
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3694 '99 AUG -6 P12:24

BASF Pharma

Re: Docket No. 99D-1149
Draft Guidance for Industry
on In Vivo Pharmacokinetics and
Bioavailability Studies and In
Vitro Dissolution Testing for
Levothyroxine Sodium Tablets

Knoll Pharmaceutical Company ("KPC" or "Knoll") has the following comments on the above-referenced draft guidance. These comments focus on two sets of issues. First, we provide comments on the draft guidance as it will be used in the context of bioavailability for new drug applications.[1] Second, we point out that the study design proposed in the draft guidance for conducting bioavailability studies is unsuitable for conducting bioequivalence studies and that FDA is required by law and its own good guidance policies to provide a full and separate opportunity for public comment on any draft guidance discussing assessment of bioequivalence of levothyroxine sodium tablets.

A. Bioavailability, Dosage Form Equivalence, and Dissolution Studies in the NDA Context.

The draft guidance is modeled after the bioavailability study design developed by KPC (formerly Boots Pharmaceuticals, Inc.) and published by Drs. Berg and Mayor.[2] The Berg-Mayor model employs the administration of a single suprapharmacologic dose of levothyroxine sodium (600 mcg) to healthy volunteers in order to produce increases over background endogenous T_4 concentrations large enough to measure. Having developed the Berg-Mayor model, Knoll is familiar with both its advantages and with certain limitations.

1. Potential Inapplicability of the Suprapharmacologic Dose. Fish et al reported that while the metabolic clearance rate of levothyroxine was constant up to 2.0mcg/kg, it increased sharply at doses above that.[3] The administered dose in the Berg-Mayor model would be approximately 8.6mcg/kg in a 70kg individual. Thus, the kinetics of the 600 mcg dose may not be directly applicable to the therapeutic range of levothyroxine.

Also, the 600 mcg dose will suppress TSH below the sensitivity of current assays. Measurement of TSH is an important and relevant determination because it reflects the concentration of metabolically available thyroid hormone at sites of cellular activity. Knoll therefore questions the desirability of using a bioavailability model that makes impossible the measurement of TSH.

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1. On December 15, 1997, KPC submitted a Citizen Petition, 97N-0314/CP2, stating that its Synthroid® levothyroxine sodium tablets are generally recognized as safe and effective and are therefore not new drugs.
2. Jeffrey A. Berg and Gilbert H. Mayor, Study in Normal Human Volunteers to Compare the Rate and Extent of Levothyroxine Absorption from Synthroid® and Levoxine®, J. Clin. Pharmacol. 1993; 33:1135-1140 (copy attached).
3. Lisa H. Fish, Harold L. Schwartz, John Cavanaugh, Michael W. Steffes, John P. Bantle, and Jack H. Oppenheimer, Replacement Doses, Metabolism and Bioavailability of Levothyroxine in the Treatment of Hypothyroidism, New England J. Med 1987; 316:764-770 (copy attached)

2. Problematic Foods. The guidance should specify that meals not include goitrogenic foods that may affect the synthesis of thyroid hormone, including turnips, cabbage, rutabaga, Brussels sprouts, mustard greens and kale.

3. Possible Need to Measure Absolute Bioavailability. Because levothyroxine sodium is available in IV dosage form, it is possible to conduct studies of absolute bioavailability, as well as the relative bioavailability study contemplated by the draft guidance. Maxon et al have published a model for doing so.[4] For patients with severe hypothyroidism accompanied by gastrointestinal hypomotility and those requiring rapid restoration of thyroid function, IV treatment may be the preferred starting form of levothyroxine. Conversion of such patients from IV to oral dosing is currently done empirically. Knowledge of absolute bioavailability of tablets will make it significantly easier for physicians to select appropriate strengths of tablets after discontinuation of IV administration.

4. Use of Baseline-Corrected Data. The draft guidance proposes to measure total T_4 and total T_3 following a single 600 mcg dose of LT_4. Under these conditions, the concentration of T_4 derived from exogenously administered LT_4 cannot be distinguished from endogenous T_4 by conventional immunoassays, and what is therefore reported is a summation effect, which is at variance from the basic premise of bioavailability as the rate and extent of absorption of exogenously administered drug. In order to measure concentrations of exogenous hormone, and in order to adjust for intersubject differences in baseline endogenous T_4 levels, the Berg-Mayor model reports only baseline-corrected data. Knoll recommends that this approach be incorporated into the draft guidance.

5. Dosage Form Equivalence Study. FDA ordinarily suggests conducting such studies using dosage strengths within the labeled dosage range. In the draft guidance, however, FDA is proposing to assess those strengths by comparing multiples of them totaling 600 mcg, an amount double the highest marketed strength and nearly five times the highest commonly prescribed strength (125 mcg). As noted above, kinetics of levothyroxine may not be linear, and so there is a real question whether these measurements are meaningful. FDA should consider instead use of the Maxon model, supra, note 4, for measuring bioavailability at therapeutic doses, which would also facilitate conducting dosage form equivalence studies at therapeutic strengths.

6. Dissolution. No direct correlation between dissolution rates and bioavailability has been established. Accordingly, there is no need to conduct dissolution studies as part of the demonstration of bioavailability in the NDA context. Until there is definitive information on the dissolution conditions that yields information on bioavailability, this section of the draft guidance should be omitted.

B. The Methodology Proposed for Bioavailability Studies is Unsuitable for Bioequivalence Studies. In any Event, FDA Must Provide a Separate Opportunity for the Public to Comment on Any Draft Guidance on Bioequivalence.

Although the Berg-Mayor model may be suitable for determination of levothyroxine bioavailability in the NDA context, it is not suitable for assessing bioequivalence. As FDA has recognized, levothyroxine sodium is a narrow therapeutic index drug,[5] which makes the issue of how best to determine bioequivalence an important one. How to demonstrate bioequivalence of levothyroxine products has also been the subject of considerable debate about the proper design and execution of such studies.

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4. H.R. Maxon, W.A. Ritschel, C.P. Volle, M.A. Eldon, I.W. Chen, M.F. Fernandez, J. Cline, and G. Mayfield, Pilot Study on the Absolute and Relative Bioavailability of Synthroid and Levothroid, Two Brands of Sodium Levothyroxine, Int. J. Clin, Pharmacol. Ther. Toxicol. 1983; 21: 379-382 (copy attached).
5. Prescription Drug Products, Levothyroxine Sodium, 62 Fed.Reg. 43535 (August 14, 1997).

With all the debate, however, no one has ever suggested that the Berg-Mayor model is appropriate to determine bioequivalence.[6] Indeed, as noted in KPC's earlier comments on this draft guidance, FDA has previously taken the position that the Berg-Mayor model is unsuitable for either bioavailability or bioequivalence.

Under Section 701(h)(1)(C) of the Food, Drug and Cosmetic Act, FDA must "ensure public participation prior to implementation of guidance documents dealing with complex scientific issues and highly controversial issues." Any guidance dealing with bioequivalence of levothyroxine products for oral administration certainly fits both categories. It would also be a Level 1 guidance under FDA's Good Guidance Practices,[7] and FDA must therefore solicit public input and provide for public participation.[8]

FDA cannot satisfy these obligations with respect to any proposed bioequivalence guidance by treating this draft guidance on bioavailability as mooting the need for a separate notice and a separate process as to bioequivalence. Bioavailability and bioequivalence have some commonalities, but many of the issues they implicate are quite different from a scientific or clinical standpoint, especially for narrow therapeutic index drugs, and, in particular, one which is endogenously produced and subject to feedback regulation. Also, many clinicians, scientists, and other members of the public who are greatly interested in the design and conduct of bioequivalence studies of levothyroxine products are indifferent to bioavailability of such products in the NDA context. They would not see any reason to comment on a draft bioavailability guidance, but would participate fully in a process designed to consider bioequivalence issues. That is another reason why a separate process is needed for bioequivalence.

Knoll appreciates the opportunity to comment on this draft guidance.

Sincerely,

Robert W. Ashworth, Ph.D.
Director, Regulatory Affairs

6. It has been and remains Knoll's view that although the Berg-Mayor model is appropriate for demonstration of bioinequivalence, it is unsuited to efforts to demonstrate bioequivalence.
7. 62 Fed. Reg. 8961 (Feb. 1997).
8. Id. at 8968.